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HYPERPLASIA OF JUXTAGLOMERULAR CELLS AND RENOMEDULLARY INTERSTITIAL CELLS AFTER RENAL ARTERIAL EMBOLIZATION IN PATIENTS WITH RENAL CELL CARCINOMA

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Renal tissue was obtained from 36 patients with renal cell carcinoma, some of whom received renal arterial embolization. The removed specimens were examined histopathologically and the concentration of some vasoactive substances in these patients was measured.

Nephrectomy alone produced no discernible changes in blood pressure, vasoactive substances determined or histopathological findings of the kidney. Renal arterial embolization raised the blood pressure in association with the elevation of plasma renin activity (PRA) and urinary prostaglandin (PG) E₂ excretion. A linear relationship was found to exist between PRA and mean blood pressure ($r=0.70$, $p<0.001$). Hyperplasia of the juxtaglomerular (JG) apparatus, and high granularity of sudan black B granules in renomedullary interstitial cells were confirmed in removed kidneys of patients who had received embolization alone.

Subsequently high renin production would be anticipated to influence overproduction of renal PG E₂ in acute ischemic kidney in patients with renal cell carcinoma, and hypertension following renal arterial embolization appears to be caused by the hyperplasia of the JG apparatus.

Key words: Juxtaglomerular cell, Renomedullary interstitial cell, Renal, carcinoma, Renal arterial embolization

INTRODUCTION

Preoperative embolization of the renal artery is undoubtedly useful for the removal of a renal mass. For inoperable primary tumors, this process can exert a beneficial effect on bleeding, pain or endocrine disturbances arising from the presence of the tumor. Reported complications include temporary hypertension, fever, necrotic tumor infection, temporary renal function impairment and accidental embolization of other organs^{11,13}. Documentation of these clinical symptoms has been somewhat neglected, since embolization of the primary tumor can be contemplated as an adjuvant to radical nephrectomy by temporal decongestion of

the tumor and reduction of its size. Renin has been assumed to be released into the circulation by several specific stimuli produced by the renal artery stenosis following renal arterial embolization and that angiotensin is then produced from blood-borne angiotensinogen in plasma. Previously we reported that acute constriction of the renal artery in a man led to hyperplastic change of the juxtaglomerular cells and the renomedullary interstitial cells, stimulating an inappropriate release of renin and renal prostaglandins¹⁶. We elucidated whether the change in plasma renin activity was related to the simultaneous alteration of urinary prostaglandin or blood pressure in patients received renal arterial embolization. The removed kidney specimen was also examined histopathologically with special

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reference to hypertension.

MATERIALS AND METHODS

Between October, 1980 and March, 1986, a total of 36 cases diagnosed histopathologically as renal cell carcinoma were studied. Nine patients underwent radical nephrectomy, and 27 subjects underwent renal arterial embolization and subsequent radical nephrectomy. Computed tomography, echographic exploration of the kidney and intravenous urography with or without nephrotomography had previously been performed for diagnostic purposes. In each case, a preliminary abdominal aortogram was obtained to aid the transfer of embolizing particles. The age of the nephrectomized group (8 men 1 woman) $[62 \pm 5$ (mean \pm S.E.) years] was similar to that of the embolization plus nephrectomized group (20 men and 7 women) $[61 \pm 3$ (mean \pm S.E.) years]. The stage of tumor was decided according to the system of Robson¹⁸⁾ in both groups: stage I, 5 cases; stage II, 1 case; stage III, 1 case and stage IV, 2 cases in the former group and stage I, 7 cases; stage II 3 cases; stage III, 3 cases and stage IV, 14 cases in the latter group, respectively. Selective catheterization was accomplished using a guide wire over which a 7-French silicon catheter was advanced to the desired location of the expedient renal artery by transfemoral approach. For the angiographic catheter, a femoral visceral A-1 (COBRA) III, or a femoral-cerebral B (SIDEWINDER) I or II (Cordis Corp. Miami, Fla, USA) was used. A coaxial system consisting of an outer 6.5-French polyethylene catheter was also used in some instances⁶⁾. Gelfoam cubes or Gelfoam powder (Upjohn Kalamazoo, Mich) was used for renal, arterial embolization. The untoward effects of renal embolization included flank pain, raised fever, nausea, vomiting, other gastrointestinal complications and hypertension. The severity of the symptoms appeared to be mostly related to the degree of infarction achieved. In most cases, radical nephrectomy was done 7 days after the emboli-

zation. Removed kidneys were dissected and fixed in 10% phosphate-buffered formalin at pH 7.4 or in Zenkel formalin. They were then stained with hematoxylin and eosin, periodic acid-Schiff, Bowie and Sudan black B.

After adaptation to the dietary environment (150~180 mEq/day of dietary sodium), 24-hour urine and blood were repeatedly collected. Plasma renin activity (PRA) was assayed by radioimmunoassay of generated angiotensin I, using the method originally devised by Katz and Smith⁹⁾ as modified by Yun et al.²¹⁾. Urinary PG E₂ excretion was determined by a radioimmunoassay originally produced by Jaffe et al.⁶⁾ and developed by Dray et al.⁵⁾ and Zawada et al.²²⁾.

Statistical analyses were done by Student's *t*-test. Changes were considered significant when *p* values were less than 0.05.

RESULTS

As shown in Fig. 1, the average blood pressure for the nephrectomized group (A) before surgery $[130 \pm 7/67 \pm 6$ (mean \pm S.E.) mmHg] remained stable following nephrectomy at one week $[133 \pm 9/61 \pm 4$ (mean \pm S.E.) mmHg] or at least 2 weeks $[126 \pm 7/61 \pm 6$ (mean \pm S.E.) mmHg]. The average blood pressures for the renal embolization and subsequent nephrectomy group (B) during the control period, one week after

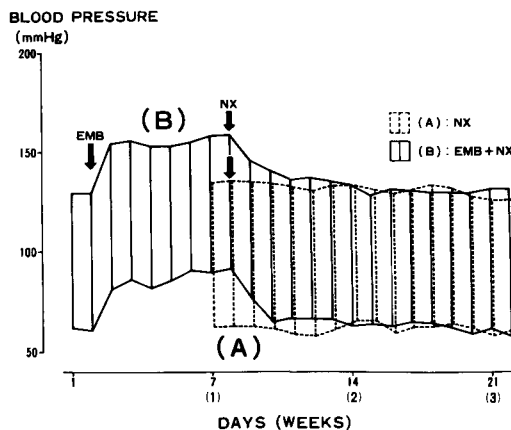


Fig. 1. The daily blood pressure in patients with renal cell carcinoma who underwent nephrectomy (NX) alone (A) or after renal arterial embolization (EMB) (B).

embolization and one week after subsequent nephrectomy were $133 \pm 4/68 \pm 6$, $158 \pm 6/94 \pm 5$ (mean \pm S.E.) mmHg], respectively. The embolization caused a 21.5% ($p < 0.001$) or 19.2% ($p < 0.001$) increase in systolic or diastolic blood pressure at one week in this group of patients, but hypertension was completely normalized 2 weeks after the nephrectomy [$132 \pm 4/58 \pm 6$ (mean \pm S.E.) mmHg].

Remarkable hyperplasia and high juxtaglomerular granularity of juxtaglomerular apparatus (JGA) were not seen in patients who had undergone nephrectomy alone. Normal appearance of the JGA noted in 7 patients (77.8%), and a slightly granule content was seen in 2 patients (22.2%). As can be seen in Fig. 2A, PRA in normally appearing JGA of nephrectomized patients [1.86 ± 0.21 (mean \pm S.E.) ng/ml/hr] was similar to that of slightly hyperplastic patients [1.85 ± 0.15 (mean \pm S.E.) ng/ml/hr] who had undergone the same operation. The level of mean blood

pressure (MBP) in the former group of patients [90 ± 5 (mean \pm S.E.) mmHg] was similar to that in the latter group of patients [82 ± 7 (mean \pm S.E.) mmHg] (Fig. 2B). As can be seen in Fig. 2C, there was no significant correlation in the regression line or coefficient between PRA and MBP.

Upon renal arterial embolization, the granularity of the JGA was enhanced except for one set of determinations. After the embolization, PRA also showed a similar increase in the histopathological analysis. Level of PRA in normally appearing JGA (Fig. 3), slight hyperplastic JGA and moderately hyperplastic JGA (Fig. 4) in patients who had undergone renal arterial embolization plus nephrectomy were 2.56 ± 0.33 , 3.82 ± 0.18 , and 4.37 ± 0.24 (mean \pm S.E.) ng/ml/hr, respectively (Fig. 2A), and level of MBPs 115 ± 3 , 116 ± 3 and 119 ± 3 (mean \pm S.E.) mmHg, respectively (Fig. 2B) and PRA was directly proportional to MBP (Fig. 2C).

Normal appearance of interstitial cells

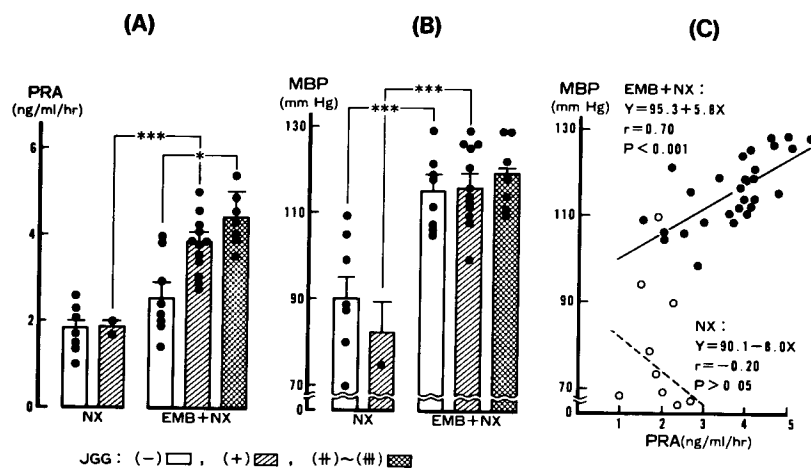


Fig. 2. A: PRA (ng/ml/hr) in patients who underwent nephrectomy alone (NX) or after arterial embolization (EMB+NX). JGG (-): Normally appearing juxtaglomerular granularity, JGG (+): Slightly hyperplastic juxtaglomerular granularity, JGG (+)(#): Marked hyperplasia of juxtaglomerular granularity. Vertical bars: \pm S.E.M. * $p < 0.05$, *** $p < 0.001$: Paired comparisons. B: Mean blood pressure (MBP) (mmHg) in patients who underwent nephrectomy alone or after renal arterial embolization. Schematic presentation and statistical analysis are the same as in Fig. 2A. C: Relationship between MBP (mmHg) and PRA (ng/ml/hr) in patients who underwent nephrectomy alone (dotted line and open circle) or after renal arterial embolization (solid line and closed circle). Schematic presentations are the same as in Fig. 2A.

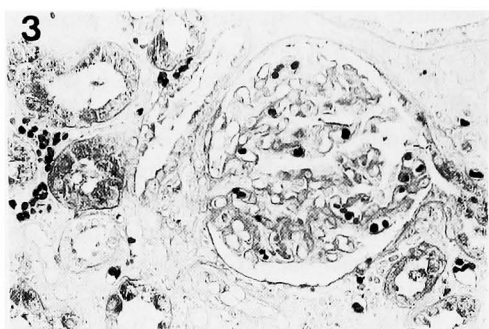


Fig. 3. Normally appearing of juxtaglomerular apparatus. HE stain, $\times 200$.



Fig. 4. Moderately hyperplastic juxtaglomerular apparatus. HE stain, $\times 200$.

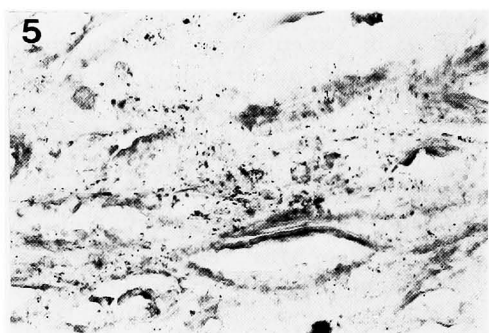


Fig. 5. Normally appearing renomedullary interstitial cells with lipid granules stained with sudan black B. Sudan black B stain, $\times 200$.



Fig. 6. Renomedullary interstitial cells with great amount of lipid granules stained with sudan black B. Sudan black B stain, $\times 200$.

with sudan black B granules in the kidney (Fig. 5) and slightly high granularity of those renal cells (Fig. 6) were found in (57.1 %) and 3 of 7 patients (42.9 %) who had undergone radical nephrectomy, respectively. Urinary PG E_2 excretion of the former group of patients [99 ± 4 (mean \pm S.E.) $\mu\text{g/day}$] was not different from that of the latter group [109 ± 9 (mean \pm S.E.) $\mu\text{g/day}$] (Fig. 7A). Renal arterial embolization raised this value ($p < 0.001$) in the former group of patients [222 ± 12 (mean \pm S.E.) $\mu\text{g/day}$] and the latter group of subjects [194 ± 8 (mean \pm S.E.) $\mu\text{g/day}$], respectively.

In patients who underwent nephrectomy after embolization, there was a quite low correlation between PRA and urinary PG E_2 excretion, but none in the subjects who underwent nephrectomy alone (Fig. 7B).

Sclerosis of interlobular artery was noted in all patients, although the extent

varied considerably from patient to patient (Fig. 8, 9). As depicted in Table 1, the degree of sclerosis was not related to the change in blood pressure following embolization or nephrectomy.

DISCUSSION

Biochemical changes following the renal embolization were appreciable within 7 days of the treatment, but they did not persist after the subsequent nephrectomy. As demonstrated in Fig. 2, the etiology of this type of hypertension following renal arterial embolization appears to be attributed to the increased liberation of renin acting on angiotensinogen to liberate angiotensin I, from which histidyl and leucine residues are cleaved by the converting enzyme to yield angiotensin II which produces potent vasoconstriction. Enhanced production of angiotensin II would lead to stimulation of aldosterone secretion

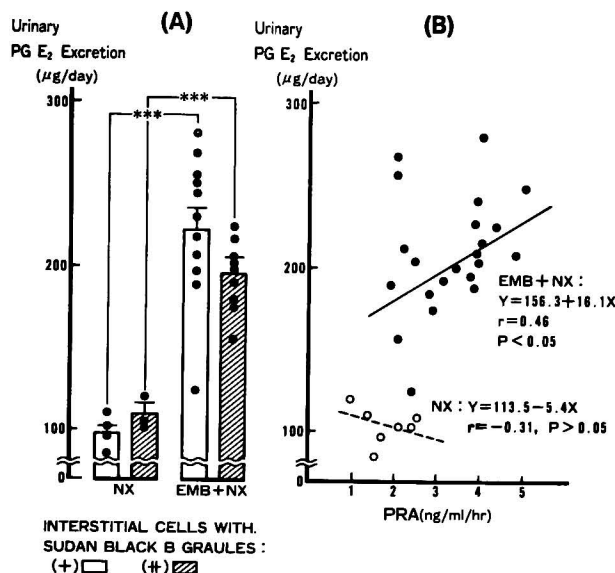


Fig. 7. A: Urinary PG E₂ excretion (μg/day) in patients who underwent nephrectomy alone or after arterial renal embolization. Schematic presentation and statistical analysis are the same as in Fig. 2A. B: Relationship between urinary PG E₂ excretion (μg/day) and PRA (ng/ml/hr) in patients who underwent nephrectomy alone (dotted line and open circle) or after renal arterial embolization plus nephrectomy (solid line and closed circle). Schematic presentations are the same as in Fig. 2A.

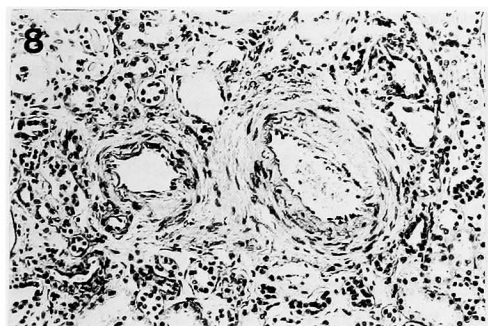


Fig. 8. Slight sclerosis of interlobular artery in a patient who had undergone nephrectomy after renal arterial embolization. HE stain ×100.

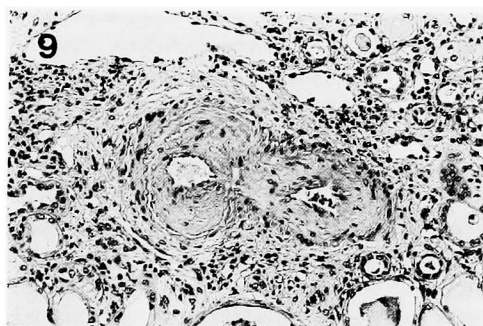


Fig. 9. Marked sclerosis of interlobular artery in a patient who had undergone nephrectomy alone. HE stain ×100.

which would raise circulating blood volume or vascular resistance and contribute to the elevation of blood pressure. Indeed, hypertrophy of JGA and high granularity of JG granules were predominantly confirmed in patients who had undergone renal arterial embolization (Fig. 2A). Recent immunochemical studies have revealed the coexistence of renin and angiotensin II in

JG cells, and ultrastructural studies and the subcellular organelle fraction have demonstrated the localization of renin and angiotensin in renin granules⁷⁾. According to Mendelsohn et al.¹³⁾, the renal tissue angiotensin II concentration was much higher than could be accounted for on the basis of circulating angiotensin II level. However, which of these factors have the

Table 1. Changes of blood pressure (BP) and sclerosis of interlobular artery in patients who received radical nephrectomy (A) and embolization plus radical nephrectomy (B).

Treatment	Degree of sclerosis	BP before treatment	BP after treatment	
			1 week	2 weeks
(A) Radical nephrectomy	++ (n = 5)	132 ± 11/70 ± 10	130 ± 10/68 ± 6	132 ± 8/64 ± 8
	+++ (n = 4)	134 ± 10/68 ± 7	* 136 ± 9/70 ± 8	*** 132 ± 8/68 ± 8
(B) Embolization plus Radical nephrectomy	+	128 ± 17/72 ± 8	* 154 ± 15/94 ± 12	* 130 ± 6/68 ± 10
	++ (n = 19)	136 ± 7/86 ± 6	158 ± 6/99 ± 5	134 ± 8/84 ± 6
	+++ (n = 5)	140 ± 4/88 ± 5	164 ± 5/102 ± 6	138 ± 4/87 ± 6

Results are shown in mean ± S.E.

*p < 0.05, ***p < 0.001: paired comparisons.

Degree of sclerosis: +; slight extent, ++; moderate extent, +++; severe extent. See detail in the text.

greatest influence is unknown. There is dispute about the origin of the angiotensin II found in the JG cells¹³. Cantin et al.³⁾ demonstrated that renin and angiotensin II coexist in the same granules. There were smaller amounts of the immunogold corresponding to renin³⁾. Under situations of ischemia the incitement is reversed with more angiotensin II and less renin. We did not perform such analysis on this type of clinical hypertension.

Intensive biosynthetic ability for PG I₂ has been detected in the inner medula of the dog kidney where the vascular blood volume is extremely poor compared with other areas¹⁹⁾. Previous studies have shown increased renal PGE₂ excretion rates and renal tissue PG intensity in patients with renal disease and in animals with renal failure^{4,10)}. Studies on the dog have shown that PG E₂ reduces renal vascular resistance²⁾ and studies on rat that I₂ causes vasodilation²⁰⁾. The predominant pathway for the inactivation of PG E₂ in animal kidney entails its transformation to PG F_{2α} by way of PG E₂ ketoreductase¹⁴⁾. A high level of urinary PG E₂ excretion associated with an increment of PRA could be observed in our patients after renal arterial embolization (Fig. 7B). In addition, high granularity was seen in sudan black B granules in interstitial cells (Fig. 6). Subsequently, it appears reason-

able to conclude from these findings that the ability of the renin-angiotensin system to cause hypertension is more effective than the effect of renal PG E₂ to reduce blood pressure. The significance of the coexistence of the hyperplastic JG apparatus and high granularity of sudan black stained granules in interstitial cells has not been assessed fully but a similar pathological finding has been observed in patients with obstructive renal artery¹⁶⁾. Does the enhanced renin-angiotensin system promote the renal PG system in patients with renal cell carcinoma after renal arterial embolization? In experimental unilateral renal hypertension, participation of central norepinephrine or vascular non-collagenous protein appears to be important for raising blood pressure^{15,17)}. Further studies are awaited.

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腎動脈塞栓術後の腎癌患者にみられる傍糸球体細胞，腎髄質間質細胞の過形成

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腎癌患者36例に腎摘除術ないしは腎動脈塞栓術兼腎摘除術を施行した。前者のみでは，血圧は不変で，測定した vasoactive substance も変化しなかった。後者の術式を施行すると，まず腎摘除術に先行して行った腎動脈塞栓術により血圧は上昇し，血漿レニン活性（PRA），尿中プロスタグランディン E_2 （PG）排泄量も増加した。しかも PRA と尿中 PGE_2 排泄量との

間に正の相関が認められた。摘除腎には，傍糸球体装置および髄質間質細胞の過形成が見られた。すなわち，腎癌患者における急速な腎虚血はレニン分泌細胞の増殖とともに PG 分泌細胞の増殖も惹起させることが推測された。

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